The ethics of placebo in clinical psychopharmacology: the urgent need for consistent regulation

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The ethics of research on humans is a topic that elicits much debate. One of the current hot topics is the ethics of the use of placebo. Strongly held beliefs in the research community diverge widely. The principle of clinical equipoise[1] requires a genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial. Acceptance of clinical equipoise necessarily implies that the use of placebo is unacceptable in any situation where there is an effective treatment.[2,3] Some have argued that preventing the use of placebo means that more patients are exposed to experimental medications that are potentially without efficacy and may have serious adverse effects (e.g., the Canadian College of Neuropsychopharmacology position paper on ethics of placebo[4]). Furthermore, examples can be found of situations in which the evaluation of potentially beneficial treatments is problematic if strict adherence to the principle of equipoise is required. For example, under clinical trial conditions, in patients with major depressive disorder, the difference between the effects of a standard treatment and placebo is small. In the absence of a placebo arm, a new treatment could appear to be of similar effectiveness to standard treatment, yet actually be no better than a placebo. Therefore, placebo should be permitted in clearly defined circumstances, even if standard treatments exist, as long as steps are taken to minimize the risk to patients and as long as the patients understand the nature of the risks they are taking.

It is unlikely that the 2 sides on the placebo debate will arrive at any consensus. Given that these strongly held and divergent views exist, there is an important need for:

- clearly written and consistent regulations that all researchers will comply with, whatever their own opinions, and
- visible and fair enforcement of the regulations.

Unfortunately, neither situation exists, especially in Canada.

One of the cornerstones of ethical human research is the World Medical Association's *Declaration of Helsinki*.[5] Paragraph 29 of the *Declaration of Helsinki* states that:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

However, the World Medical Association Council issued, in October 2001, a note of clarification on paragraph 29. This clarification states that a placebo-

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controlled trial may be ethically acceptable, even if proven therapy is available, under various circumstances including:

> Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.

This "clarification" directly contradicts paragraph 29 and, therefore, confuses rather than clarifies the situation.

In Canada, human research is governed by the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans,*[6] a joint policy of the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council. Article 7.4 of this document states that "The use of placebo controls in clinical trials is generally unacceptable when standard therapies or interventions are available..." However, a placebo may be used in the following clearly defined circumstances:

a. There is no standard treatment;
b. Standard therapy has been shown to be no better than placebo;
c. Evidence has arisen creating substantial doubt regarding the net therapeutic advantage of standard therapy;
d. Effective treatment is not available to patients due to cost constraints or short supply;
e. In a population of patients who are refractory to standard treatment and for whom no standard second-line treatment exists;
f. Testing add-on treatment to standard therapy when all subjects in the trial receive all treatments that would normally be prescribed; or
g. Patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and when withholding such therapy will not lead to undue suffering or the possibility of irreversible harm of any magnitude.[6]

This policy clearly prohibits the use of placebo, for example, in the test of a new antidepressant or anxiolytic against a standard drug and placebo. However, as pointed out recently by Weijer,[7] trials of this type continue in Canada. Weijer mentions that a Research Ethics Board (REB) of which he was a member turned down a multicentre, randomized controlled trial protocol designed to compare a new selective serotonin uptake inhibitor (SSRI), a standard SSRI and placebo. However, 16 other REBs in Canada approved the protocol. We have had similar experiences in our work on 2 other REBs. How can this situation exist? As Weijer[7] points out, the *Tri-Council Policy Statement* may conflict with the requirement of regulatory agencies. He quotes a letter from Health Canada's Therapeutic Products Directorate stating:

> We believe judicious use of placebo controlled trials to establish unequivocally the efficacy of a new drug, together with a comprehensive risk management protocol and appropriate informed consent, is ethical. To use an inconclusive trial design when a conclusive trial design is possible, is unethical.[7]

If evidence from placebo-controlled trials is necessary to get various drugs such as antidepressant and anxiolytics approved in Canada, this obviously places pressure on REBs to approve such trials. However, if Health Canada approves new drugs on the basis of evidence that can not be obtained in Canada according to current regulations, then either the evidence must be obtained in Canada in violation of current regulations, or the evidence must be obtained in studies carried out in other countries. Neither option is acceptable. The current situation may be solved by the National Placebo Initiative, which is now in phase 1 of a 3-phase initiative that will eventually produce recommendations to Health Canada and the Canadian Institutes of Health Research about how to amend the regulations of Health Canada and the *Tri-Council Policy Statement* to make them consistent.[8]

The US Food and Drug Administration (FDA) policy, Guidance Document E10 *Choice of Control Group and Related Issues in Clinical Trials*, includes the statement that:

> In cases where an available treatment is known to prevent serious harm, such as death or irreversible morbidity in the study population, it is generally inappropriate to use a placebo control. ... In other situations, where there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort as a result, provided the setting is noncoercive and patients are fully informed about available therapies and the consequences of delaying treatment.[9]

The FDA policy also mentions that placebo-controlled

trials may be necessary in conditions "in which drugs considered effective cannot regularly be shown superior to placebo in well-controlled trials."[9] Conditions mentioned include depression and anxiety.

The National Placebo Initiative is an encouraging development, but it does not solve the problem of the lack of enforcement of current regulations. How can REBs approve placebo-controlled trials that do not comply with the *Tri-Council Policy Statement*? No clear answer can be given to this question. However, the lack of accountability of REBs is certainly a factor. Article 1.4 of the *Tri-Council Policy Statement* states that REBs shall be established by the highest levels of the institution. Boards of universities or hospitals often delegate this responsibility and do not often take an active role in assessing how REBs function or assessing whether REBs comply with all the details of regulatory documents such as the *Tri-Council Policy Statement*. This is unfortunate given that REB decisions have financial implications for the institution. The overhead paid by a drug company to an institution to carry out a study benefits that institution. An institution will benefit more financially if an REB approves a placebo-controlled study than if it turns it down. There is no suggestion that REBs might be influenced by such considerations, but the fact that REB decisions can have financial implications reinforces the need for transparency.

The regulation of human research differs greatly from the regulation of animal research in Canada. The Canadian Council on Animal Care (CCAC) carries out site visits to universities and hospitals performing animal research, usually every 3 years. Criteria used by the CCAC on site visits are specified in detail[10] and include adherence to the *Terms of Reference for Animal Care Committees* and the CCAC *Guide to the Care and Use of Experimental Animals*. CCAC makes recommendations for changes on the basis of site visits and follows up on whether the changes have been made. If CCAC gives an organization the status of noncompliance, the major research funding agencies in Canada can withdraw their funding from that institution. The contrast between the close appraisal of animal research and the laissez-faire control of human research needs no comment.

How should the current situation be changed? First, bodies such as the World Medical Association should ensure that all aspects of their policies are consistent and give clear guidance on complex issues such as the use of placebos. Second, in Canada, the National Placebo Initiative has to arrive at recommendations that can be used as the basis for the policies of Health Canada and the Tri-Council. Third, the granting councils need to set up a system that ensures that REBs do, in fact, follow the *Tri-Council Policy Statement*. The way the CCAC regulates animal research seems to be a workable model. Without such changes, the credibility of all relevant organizations will be damaged. The most likely result will be heavy-handed governmental regulations that, in the long run, will not meet the needs of patients or clinical researchers.

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